IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Ingo Konetzki *et al.*	Examiner:	D.Margaret Seaman
Serial No.:	10/717,868	Group Art Unit:	1625
Filed:	November 19, 2003	Docket:	1/1428

For: TIOTROPIUM-CONTAINING PHARMACEUTICAL COMBINATION FOR INHALATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF MICHAEL PAUL PIEPER UNDER 37 C.F.R. § 1.132

Sir:

I, Michael Paul Pieper, declare that:

1. I have studied Veterinary medicine at the University (School of Veterinary Medicine Hannover) Hannover, Germany from 1986 to 1991 (Degree: board certified veterinarian).

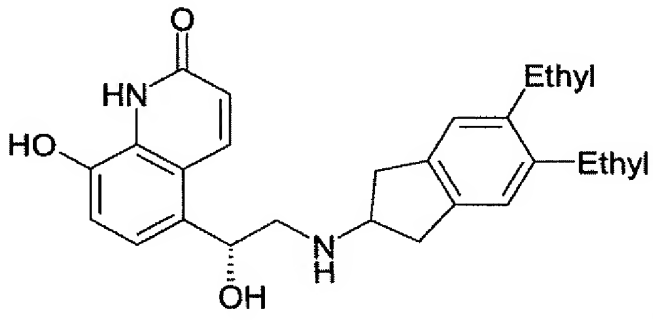
2. I did my doctoral thesis in Pharmacology from 1992 to 1994 and received a VMD (Dr. med. vet.) from the School of Veterinary Medicine Hannover, Hannover, Germany in 1994.

3. Since 1994, I have been employed by Boehringer Ingelheim, presently in the Department of Pulmonary Research of Boehringer Ingelheim Pharma GmbH & Co. KG, Germany.

4. I am a coinventor of the above-identified patent application and I am familiar with the above-identified patent application (hereinafter "the Konetzki *et al.* application").

5. I am familiar with the U.S.P.T.O. Office Action dated June 13, 2003 and the prior art references cited therein: WO 00/75114 and WO 02/45703.

6. Under my responsibility and control, investigations with inhalative administration of the bronchospasmolytic test compounds tiotropium bromide and the compound of formula (2a)



(2a),

in form of its R-enantiomer and as the maleinat acid addition salt (hereinafter "compound (2a)") were conducted according to the experimental protocol described in ANNEX 1.

7. The results of experimental tests according to the protocol of ANNEX 1 are summarized in ANNEX 2. Tiotropium as well as compound (2a) induced a time dependent protection against ACh-induced bronchoconstrictions. Tiotropium and compound (2a) initially reduced the ACh-induced bronchoconstrictions by 40% and 37%, respectively. Over 24 hours, these effects, however, attenuated. A maximally expected additive effect was calculated adding bronchoprotection values of both compounds for each time point (see ANNEX 2, table column C). To summarize the experimental results above, the combination tiotropium bromide with compound (2a) reduced the ACh-induced bronchoconstrictions significantly more potent than the reduction of the ACh-induced bronchoconstrictions achieved using tiotropium or compound (2a). Furthermore, the reduction of the ACh-induced bronchoconstrictions of the combination was greater than the calculated sum of the effects of each single component administered alone.

8. From the above experiments and results, I conclude that the combinations according to the invention of the above-identified patent application, as exemplified by tiotropium bromide and compound (2a), display an unexpected beneficial and synergistic effect which is even greater than the calculated sum of the effects of each single component administered alone.

11. Furthermore, I conclude that these surprising properties of the combinations according to the invention of the above-identified patent application were neither taught, suggested, nor deducible by the cited prior art. Moreover, I conclude that these findings would have been both surprising and unexpected to one of ordinary skill in the art at the time the invention was made.

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: January 19th, 2007 Signature: _____

(Michael Paul Pieper)

ANNEX 1

Method for the Determination of Bronchoprotection Against Acetylcholine-Induced Bronchospastic Collapse in male beagle dogs

Animals were anesthetized with an intravenous bolus of 10 mg/kg propofol (2 % solution) and ventilated using an endo-tracheal tube. Anaesthesia was maintained by a continuous i.v. infusion of propofol (30 mg/kg/h). The endotracheal tube was connected to a heated pneumotachograph (Fleisch Nr.1, Hugo Sachs Elektronik, March-Hugstetten) in order to measure lung function measurement. Pulmonary resistance was calculated from the simultaneous measurement of transpulmonary pressure and respiratory flow using the isovolumetric method from the respiratory flow calculator of the Notocord software.

Measurements for respiratory resistance, respiratory pressure and dynamic lung compliance were taken prior to the administration of the test compounds (single compounds or drug combinations, respectively) to establish the baseline values. Further measurements were made 10 min, 30 min, 6 hours, 12 hours and 24 hours after administration of the test compound(s). Compounds were administered by inhalation using a new soft mist inhaler (Respimat®, Boehringer Ingelheim Pharma KG) into the endo-tracheal tube.

At each time point bronchoconstriction was induced by i.v. administration of 10 µg/kg acetylcholine (= ACh-challenge). The inhibitory effect was expressed as the percent inhibition calculated using the mean of the two responses to ACh-challenge prior to administration of the compounds. Between the last 3 measurements time points the dogs were allowed to awake.

Dogs were randomized into tree groups each consisting of n=3 animals. Group A received 1.0 µg tiotropium bromide, group B received 48 µg compound (2a) and group C received the combination thereof.

ANNEX 2

Results obtained according to the test protocol of ANNEX 1

In the table below the effects of tiotropium bromide (1 µg/kg) on ACh-induced bronchoconstriction in anaesthetized beagle dogs are outlined in column A, effects of compound (2a) (48 µg/kg) are outlined in column B and the effects of the combination of tiotropium with compound (2a) are outlined in column D. The calculated sum of A+B is shown in column C. Expressed are means of 3 dogs per group.

time	A		B		C	D	
[h]	Mean	SEM	Mean	SEM		Mean	SEM
0.167	8.1	7.4	37.5	2.9	45.7	59.0	6.5
0.5	40.6	11.5	37.0	3.5	77.7	74.5	6.2
6	35.2	7.8	24.0	1.9	59.2	71.2	5.0
12	15.1	8.5	9.1	4.6	24.3	44.2	11.9
24	7.8	4.0	2.7	2.0	10.5	32.3	9.2

The graphic illustration of the results is outlined below.